



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Journal Pre-proof

Acute genital ulceration after SARS-CoV-2 vaccination and infection

Tina Hsu, MD, Jacquelyn R. Sink, MD, Veronica I. Alaniz, MD, MPH, Lida Zheng,  
Anthony J. Mancini, MD



PII: S0022-3476(22)00319-5

DOI: <https://doi.org/10.1016/j.jpeds.2022.04.005>

Reference: YMPD 12932

To appear in: *The Journal of Pediatrics*

Received Date: 8 March 2022

Accepted Date: 7 April 2022

Please cite this article as: Hsu T, Sink JR, Alaniz VI, Zheng L, Mancini AJ, Acute genital ulceration after SARS-CoV-2 vaccination and infection, *The Journal of Pediatrics* (2022), doi: <https://doi.org/10.1016/j.jpeds.2022.04.005>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc.

## Acute genital ulceration after SARS-CoV-2 vaccination and infection

Tina Hsu, MD<sup>1</sup>

Jacquelyn R. Sink, MD<sup>2</sup>

Veronica I. Alaniz, MD, MPH<sup>3</sup>

Lida Zheng<sup>4</sup>

Anthony J. Mancini, MD<sup>5,6</sup>

### Author Affiliations:

1. Division of Dermatology, John H. Stroger Jr. Hospital of Cook County, Chicago, IL
2. Northwestern Medicine Dermatology Regional Medical Group, St. Charles, IL
3. Section of Pediatric and Adolescent Gynecology, Children's Hospital Colorado, Aurora, CO
4. Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL
5. Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
6. Departments of Pediatrics and Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL

### Corresponding Author:

Jacquelyn Sink, MD, Northwestern Medicine Dermatology Regional Medical Group, 2900 Foxfield Rd, Suite 101, St. Charles, IL 60174. Email: [jsink@nm.org](mailto:jsink@nm.org)

**Keywords:** vulvar ulceration; non-sexually related genital ulcers; Lipschütz ulcers; COVID-19; COVID-19 vaccination; SARS-CoV-2

**Word Count:** 1,627

**Figure Count:** 0

**Reference Count:** 7

**Funding:** None.

**Declaration of Interest:** The authors declare no conflicts of interest.

## **ABSTRACT**

Reactive, non-sexually related acute genital ulceration (AGU), also known as Lipschütz ulcer, is a non-sexually related ulceration involving the vulva, most commonly affecting girls and adolescent women in response to infection. Herein, we describe three female patients with AGU occurring after SARS-CoV-2 vaccination or natural infection.

## INTRODUCTION

Reactive, non-sexually related acute genital ulceration , also known as Lipschütz ulcer, is a non-sexually related ulceration involving the vulva, most commonly affecting girls and adolescent women. Although generally a diagnosis of exclusion, AGU has been reported following infections, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza A and B, adenovirus, and *Mycoplasma pneumoniae*. reactive AGU has been now reported in the setting of SARS-CoV-2 infection. Herein, we report three patients with AGU presumably triggered by SARS-CoV-2 vaccination or infection.

## CASE REPORT

### Patient #1

A 12-year-old otherwise healthy female presented with painful vulvar ulcerations that had been present for approximately five days. Review of systems was positive for dysuria and hematuria. She was initially evaluated by her pediatrician and empirically treated with oral nitrofurantoin, fluconazole, and phenazopyridine for suspected urinary tract infection. She was then referred to pediatric dermatology for further evaluation and treatment due to lack of improvement. She was otherwise healthy and was not taking any other medications, denied any history of sexual activity, and had no prior history of oral ulcers, inflammatory bowel disease, or autoimmune disease. the family reported that the patient had received her second dose of the Pfizer-BioNTech SARS-CoV-2 vaccine approximately 48 hours prior to symptom onset. The day following vaccination, she also developed subjective fevers, fatigue, and malaise lasting 24 hours.

On physical examination, there were approximately 2 x 2 cm well-circumscribed, shallow ulcers with yellowish sloughing and purulent exudate on opposing surfaces of the bilateral labia minora. Significant labial edema was present. Her oral mucosae were clear.

Laboratory findings were notable for normal complete blood count and comprehensive metabolic panel, and negative urine culture. Urinalysis demonstrated large leukocyte esterase, 20-29 WBC /hpf, and moderate mucus. Lesional HSV-1 and HSV-2 PCR, Trichomonas/Gardnerella/Candida DNA probe, EBV antibody panel, respiratory viral panel, and SARS-CoV-2 PCR were negative. These clinical and laboratory findings were supportive of the diagnosis of reactive AGU triggered by the SARS-CoV-2 vaccine.

The patient was given topical clobetasol 0.05% ointment twice daily, lidocaine 2% jelly every 4-6 hours as needed, oral acetaminophen and ibuprofen as needed, and sitz baths with improvement of her symptoms. Ulcers healed over the course of two weeks.

## **Patient #2**

A 14-year-old female presented to the emergency department with two days of severe vulvar pain and ulceration. Onset of symptoms occurred three days after the patient received her second dose of the Pfizer-BioNTech SARS-CoV-2 vaccine and was associated with low grade fevers. This presentation was her second episode of genital ulceration, the first having occurred several months prior following fever, headaches, and body aches. SARS-CoV-2 PCR, EBV serologies, and HSV PCR performed at the time of her first episode were all negative.

Physical examination was notable for left labial swelling and two ulcerations on the inner aspects of the left and right labia near the introitus. The left-sided ulcer was approximately 4 cm in diameter with an overlying grey eschar and the right-sided ulcer was 3 cm. No additional

evaluations were performed in the emergency department, as it was felt her presentation and examination were consistent with reactive, non-sexually related AGU.

The patient was treated with clobetasol 0.05% ointment twice daily, lidocaine 2% gel, oral acetaminophen and ibuprofen as needed, oral nortriptyline, and vulvar care with sitz baths. She had no improvement at follow up three days later and therapy was changed to lidocaine 5% ointment and an oral prednisone with taper (20 mg twice daily for 5 days followed by 20 mg once daily for 5 days) was prescribed. Her symptoms improved. Four weeks later, the ulcers were nearly healed.

Given the recurrent nature of her symptoms, she was referred for a rheumatology Evaluation included antinuclear antibody (ANA) profile, rheumatoid factor, myeloperoxidase antibodies, serine protease IgG, c-ANCA, p-ANCA and complement levels. All were normal or negative. EBV IgG and IgM antibodies were negative. HLA-B 27 antigen, fecal calprotectin, and eye examination were negative or normal.

Approximately six months later, the patient developed a third occurrence of labial ulcers, which occurred 24 hours after testing positive for SARS-CoV-2. Her symptoms included fever, chills, and headaches. She was again treated with topical lidocaine 5% ointment, oral acetaminophen and ibuprofen as needed, and topical clobetasol 0.05% ointment. At four week follow up, she was experiencing discomfort, but the ulcers were nearly healed.

### **Patient #3**

A 29-year-old female with history of asthma was referred to the Dermatology Clinic by Infectious Diseases consultants for recurrent genital ulcers, to assess for Behcet disease. The patient endorsed a history of two preceding episodes of genital ulceration, the first occurring

eight years prior to presentation and the second approximately one year prior. The latter episode was associated with a positive rapid antigen SARS-CoV-2 test.

The patient initially evaluated in the Infectious Diseases Clinic after developing ulcers of the labia minorae, each measuring up to one cm in diameter, that began 24 hours following her first dose of Moderna SARS-CoV-2 vaccine. She also complained of fevers and chills for two days following her vaccination. Lesional specimens for HSV-1 and HSV-2 PCR were negative. Per the patient, EBV and CMV IgG had been positive in 2013; repeat testing was not obtained during this presentation. She denied any history of penetrative vaginal intercourse. She had a history of oral aphthosis and HSV but denied a history of inflammatory bowel disease, pathergy at sites of needle sticks performed to draw blood, or ocular symptoms.

After her second dose Moderna-SARS-CoV-2 vaccine she presented to the Dermatology Clinic for evaluation of two genital lesions that started within 48 hours of vaccination and requested a skin biopsy to exclude infection. On her labia minorae, there were two erythematous, small erosions measuring 2 mm and 5 mm with surrounding white hyperkeratosis. Given the onset of symptoms that day, early evolving ulceration was suspected. Biopsy was performed and revealed spongiotic dermatitis with a mixed infiltrate of lymphohistiocytic cells, neutrophils and plasma cells in the dermis. In situ hybridization for Epstein-Barr virus encoding region was negative. CMV, Gram and DPAS stains also were negative. The patient was treated symptomatically with clobetasol 0.05% ointment twice daily, and the lesions resolved. She was encouraged to use L-lysine for her recurrent oral aphthous ulcers.

Of note, the patient considered changing from Moderna to the Pfizer BioNTech SARS-CoV-2 vaccination prior to her third dose. Given case reports in the literature of AGU seen after Pfizer BioNTech vaccination, she opted to continue with Moderna. At follow up, she did report



minor genital ulcerations following her booster but did not seek care due to the mild severity of symptoms.

## DISCUSSION

acute genital ulceration most commonly affects peri-pubertal and adolescent females. The ulcers are usually well-demarcated, deep, and tender to palpation. Classically, they present in a bilateral and symmetric pattern, often described as “kissing” lesions. These lesions are painful and can lead to urinary retention, and patients may require hospitalization for pain management and indwelling Foley catheter. Fortunately, AGU is a self-limited condition and is rare. Treatment is primarily supportive with local wound care, sitz baths, and pain management with oral analgesics and topical anesthetics. Topical steroids and short courses of oral steroids may be considered in refractory cases.<sup>1</sup> Given its appearance and relative rarity, reactive AGU often is misdiagnosed as a sexually acquired disease which can lead to significant psychological distress, especially in patients who may not be sexually active. The differential diagnosis for AGU includes infectious etiologies such as syphilis or HSV, autoimmune conditions such as Behcet disease or inflammatory bowel disease, and other inflammatory conditions such as erosive lichen planus, lichen sclerosus, or fixed drug eruption.

AGU has been linked to several infections, including EBV, CMV, influenza A and B, adenovirus, and *Mycoplasma pneumoniae*. Falkenhain-Lopez et al described the first reported case of painful genital ulcers along with a single oral aphtha in a 41-year-old woman in the setting of PCR-confirmed SARS-CoV-2 infection.<sup>2</sup> Symptoms resolved following a course of oral prednisone. Additional cases of AGU presenting in adolescent girls associated with SARS-CoV-2 infection have been reported by Krapf et al and Huguelet, et al, respectively. In the latter

patients, symptoms were refractory to oral corticosteroid therapy, and patients required hospitalization for pain control and immunosuppressants, prior to resolution of symptoms.<sup>1,3</sup>

There have been a variety of dermatologic conditions reported in association with SARS-CoV-2 infection, as well as in response to SARS-CoV-2 vaccines. Specifically, mRNA vaccines against SARS-CoV-2 have been linked to injection site reactions, urticaria, angioedema, pernio, pityriasis rosea-like eruptions, bullous pemphigoid, erythromelalgia, and morbilliform eruptions.<sup>4</sup> A review of the literature revealed three cases of vulvar aphthous ulcers following the Pfizer-BioNTech SARS-CoV-2 vaccine.<sup>5-7</sup> These patients initially experienced mild, flu-like symptoms following administration of the vaccine and subsequently developed vulvar ulcers within one week, with unremarkable evaluations for infectious and autoimmune causes.

We report three patients with AGU presumably triggered by SARS-CoV-2 infection or mRNA vaccination against SARS-CoV-2. Given the current environment of misinformation and distrust surrounding vaccines, it is important to accurately report adverse side effects related to the SARS-CoV-2 vaccine. Adding more information to the medical literature regarding potential side effects of SARS-CoV-2 vaccines will allow providers to be better equipped to counsel patients should symptoms occur, including the self-limited nature of AGU, as well as to avoid potentially unnecessary diagnostic evaluations. Moreover, given the possible repercussions of misdiagnosing this condition, healthcare providers should be aware of AGU and its possible rising incidence given the prevalence of both natural SARS-CoV-2 infection and vaccination.

## REFERENCES

1. Krapf JM, Casey RK, Goldstein AT. Reactive non-sexually related acute genital ulcers associated with COVID-19. *BMJ Case Rep* 2021 May 5;14(5):e24265.
2. Falkenhain-López D, Agud-Dios M, Ortiz-Romero PL, Sánchez-Velázquez A. COVID-19-related acute genital ulcers. *J Eur Acad Dermatol Venereol* 2020;34(11):e655-e656.
3. Chistl J, Alaniz VI, Appiah L, Buyers E, Scott S, Huguelet PS. Vulvar Aphthous Ulcer in an Adolescent with COVID-19. *J Pediatr Adolesc Gynecol* 2021 Jun;34(3):418-420.
4. McMahon DE, Kovarik CL, Damsky W, et al. Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: A registry-based study. *J Am Acad Dermatol* 2022 Jan;86(1):113-121.
5. Drucker A, Corrao K, Gandy M. Vulvar Aphthous Ulcer Following Pfizer-BioNTech COVID-19 Vaccine - A Case Report. *J Pediatr Adolesc Gynecol* 2021 Oct 28;S1083-3188(21)00325-9. Online ahead of print.
6. Wojcicki AV, O'Flynn O'Brien KL. Vulvar Aphthous Ulcer in an Adolescent After Pfizer-BioNTech (BNT162b2) COVID-19 Vaccination. *J Pediatr Adolesc Gynecol* 2021 Oct 25;S1083-3188(21)00304-1. Online ahead of print.
7. Popatia S, Chiu YE. Vulvar aphthous ulcer after COVID-19 vaccination. *Pediatr Dermatol* 2022 Jan;39(1):153-154.